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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/716,054	11/17/2000	Gerald R. Crabtree	STAN-166	7611

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EXAMINER	
COOK, LISA V	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 10/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/716,054	CRABTREE ET AL.	
	Examiner	Art Unit	
	Lisa V. Cook	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 16-24* is/are pending in the application.

4a) Of the above claim(s) *1-3* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/19/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 28 May 2004 has been entered.

REJECTIONS WITHDRAWN

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

2. Claims 16-24 are withdrawn from rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record in paper #23. Applicants have corrected the noted deficiencies have been obviated by amendment or arguments.

3. The rejections of record in paper #23 under 35 USC 102(b) and 35 USC 103(a) have been reconsidered and are withdrawn.

NEW GROUNDS OF REJECTIONS

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 16-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically claims 16-24 are drawn to a method of inhibiting a binding event in a host (*in vivo*) via the administration of an effective amount of a non-naturally occurring bifunctional inhibitor molecule. Although the specification is enabling for the production and *in vitro* utility of non-naturally occurring bifunctional inhibitor molecules (See assay design and results - pages 20-21), it does not reasonably provide enablement for inhibiting protein-protein interactions *in vivo* with said non-naturally occurring bifunctional molecule.

Firstly, the development of non-naturally occurring/synthetic bifunctional molecules with binding characteristics of interest necessitates several conditions which have not been described in the instant specification. In one instance, the prior art discloses that the development of inhibitors which can bind by both an active site specific interaction to a primary binding site and by a structure nonspecific hydrophobic interaction to a second site (bifunctional or bispecific molecules) requires several parameters to produce the intended binding specificity.

These parameters include; a crystal structure of the enzyme with the bound primary inhibitor, there must be a relatively "open" active site, to permit access to the active site, and the linker must introduce few unfavorable enthalpic and entropic interactions into the bound state. See Jein et al., J Med Chem., 1994, 37, 2100-2105, especially scheme 1 and page 2103, 2nd column 2nd paragraph. These parameters have not been addressed by the instant disclosure. Therefore one of skill in the art would not be able to predict the inhibition by binding of the claimed bifunctional molecule *in vivo*.

Secondly, the specification fails to teach the use of the claimed bifunctional inhibitor molecules in a living organism or host, such that an effective inhibition response is generated. The art has established that the successful production of bifunctional molecules and their utility in assay protocols does not predict their behavior in living animals or a host. In other words, the bifunctional molecule must be evaluated in a host in order to determine efficacy or inhibition effects. See Kuduk et al. Bio & Med Chemistry Letters, 10, 2000, 1303-1306, in particular page 1305, 2nd column Conclusion, 2nd paragraph.

Further, the art teaches that successful *in vitro* bifunctional construct binding is not always indicative of the *in vivo* results exhibited by that same bifunctional molecule. For example, see Peipp and Valerius page 510 – Conclusion, wherein "Results from clinical trials (in vivo effective dosage) with bispecific antibodies are less encouraging". Peipp and Valerius, Biochemistry Society Transactions, 2002, Volume 30, part 4, pages 507-511.

Accordingly, the specification does not provide substantive evidence that the claimed bifunctional molecules are capable of inhibiting a protein-binding event *in vivo*. This demonstration is required for the skilled artisan to be able to use the claimed bifunctional molecules for their intended purpose of preventing protein binding.

Without this demonstration, the skilled artisan would not be able to predict the outcome of the administration of the claimed bifunctional or bispecific non naturally occurring compositions.

The ability to reasonably predict the capacity of a single non -naturally occurring bifunctional molecule to prevent protein-protein interaction in vivo is problematic. Unfortunately, the art is replete with instances where even well characterized compositions that induce an in vitro response fails to elicit *in vivo* utility. See Waldmann, Science, Vol.252, 21 June 1991, pages 1657-1662, in particular page 1657 – 2nd column, wherein antibodies binding therapy has proven elusive and only one monoclonal antibody has been licensed for clinical utility. Accordingly, the art indicates that it would require undue experimentation to formulate and use a successful binding composition with out prior demonstration of efficacy.

Thirdly, *in vivo* testing or administration to a host entails considerations for host/patient tolerance, differences, validation, and monitoring; which are not set forth in the disclosure. The disclosure merely outlines that the non-naturally occurring bifunctional molecule may be used to treat a variety of diseases, including cellular proliferation, autoimmune disease, cardiovascular diseases, hormonal abnormality, infectious disease, and the like without any supporting data/experimentation. See page 19 lines 24-35.

However, Tockman et al. (Cancer Research 52:2711s-2718s, 1992) teach considerations necessary for a suspected cancer antibody biomarker (intermediate end point marker) to have efficacy and success in a clinical application. See page 2716s. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to other compositions being administered and tracked in a host/patient.

Tockman teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials, see abstract.

Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** (emphasis added) can be used for population screening (p. 2713s, column 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. "This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point [marker]", see page 2714s, column 1, Biomarker Validation against Acknowledged Disease End Points section. Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials, see page 2716s, column 2, Summary section.

Tockman reiterates that the predictability of the art in regards to cancer prognosis and the estimation of life expectancies within a population with a disease or disorder are highly speculative and unpredictable.

It has been set forth above that 1) the experimentation required to generate a non-naturally occurring bi-functional molecule which provides binding inhibition such that it would prevent target binding in a living host would be great as 2) there are no immunological experiments provided to demonstrate that the claimed bifunctional compositions are capable of mounting an efficient inhibition response and, more importantly, there are no challenge experiments to demonstrate that a person immunized with any one of the claimed compositions would be treated/protected from a disease. There are no protocols provided which demonstrate which bifunctional molecules would be effective in immunization, nor are there any protocols detailing the amount of the bifunctional compositions needed to inhibit protein-protein interaction or mount a sufficient immune response in disease treatment, 3) there are no working examples provided in the instant specification, 4) the nature of the invention is a method for producing a non-naturally occurring bifunctional molecule which would provide binding inhibition and treatment in a host, 5) the relevant skill of those in the art is high yet 6) the state of the prior art has been shown to be highly unpredictable as evidenced by prior art afore mentioned, and lastly 7) the claims broadly encompass the administration of compositions to a host (in vivo) to target protein prevent binding in the host, it is therefore set forth that one of skill in the art could not make and/or use the invention without undue experimentation.

Based on the analysis and the teachings presented above it would require undue experimentation for the skilled artisan to practice this invention because there is no support in the specification for the enablement of the broadly claimed invention.

Therefore, in view of the insufficient guidance in the specification, extensive experimentation would be required to enable the claims and to practice the invention as claimed.

Response to Argument

Applicant arguments against the references of Varshavsky and Poulett et al. are MOOT because the rejections have been withdrawn.

5. For reasons aforementioned, no claims are allowed.

Remarks

6. Prior art made of record and not relied upon is considered pertinent to the applicant's disclosure:

A. Weiderrecht et al. (U.S. Patent#5,457,182) teach binding interactions involving FK-506 and FKBP12.6.

B. Maragarnore et al. (U.S.Patent#5,242,810) disclose bifunctional inhibitors of platelet activation and thrombin.

7. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 – Central Fax number is (703) 872-9306, which is able to receive transmissions 24 hours/day, 7 days/week. In the event Applicant would like to fax an unofficial communication, the Examiner should be contacted for the appropriate Right Fax number.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (571) 272-0816. The examiner can normally be reached on Monday - Friday from 7:00 AM - 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (571) 272-0823.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see httpr//pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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